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(54) Title: TRIPTOLIDE ANALOGS FOR THE TREATMENT OF AUTOIMMUNE AND INFLAMMATORY DISORDERS

(57) Abstract: The present invention provides synthetic methods and compositions for treatment of autoimmune and anti-inflammatory disorders comprising administering an effective amount of a derivative of triptolide alone or in combination or alternation with other anti-autoimmune or anti-inflammatory compounds.

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TRIPTOLIDE ANALOGS FOR THE TREATMENT OF AUTOIMMUNE AND INFLAMMATORY DISORDERS

FIELD OF THE INVENTION

The present invention is in the area of pharmaceutical chemistry and specifically relates to novel compounds and pharmaceutical compositions for the treatment of autoimmune and inflammatory disorders. This application claims priority to U.S.S.N. 60/237,557, filed on October 2, 2000.

BACKGROUND OF THE INVENTION

Autoimmune and inflammatory diseases affect more than fifty million Americans. The immune system functions as the body's major defense against diseases caused by invading organisms. This complex system fights disease by killing invaders such as bacteria, viruses, parasites or cancerous cells while leaving the body's normal tissues unharmed. The immune system's ability to distinguish the body's normal tissues, or self, from foreign or cancerous tissue, or non-self, is an essential feature of normal immune system function. A second essential feature is memory, the ability to remember a particular foreign invader and to mount an enhanced defensive response when the previously encountered invader returns. The loss of recognition of a particular tissue as self and the subsequent immune response directed against that tissue produce serious illness.

Inflammation is involved in a large number of physiological and pathological conditions affecting animals and humans. Inflammatory responses can usually be traced to an immune response to an antigen, allergen, irritant, endotoxin or to tissue damage. The process is complex, involving a large number of components, many of which display pleiotropic effects, many of which are amplifiers or inhibitors of other components. While many instances of an inflammatory response are well-controlled and self-limited, many pathologic conditions arise from uncontrolled or inappropriate responses, resulting in both acute and chronic conditions.

As a result of basic research in molecular and cellular immunology over the last ten to fifteen years, approaches to diagnosing, treating and preventing these immunological based diseases have been changed forever. By dissecting the individual components of the immune system, those cells, receptors and mediators that are critical to the initiation and progression of immune responses have been, and continue to be, elucidated. Crystallographic analysis of proteins encoded in the major histocompatability complex, identification of an antigen-specific T cell receptor, and development of a basic understanding of the complex cytokine network have all contributed to a revolution in immunology. Various immunosuppressive agents have proved to be useful in the prevention of transplantation rejection and in the treatment of autoimmune diseases such as rheumatoid arthritis, nephritis, uveitis, thyroiditis, and early stage of insulin dependent diabetes mellitus, systemic lupus erythematosus, psoriasis and inflammatory bowel disease.

The immune system when operating normally is involved in precise functions such as recognition and memory of, specific response to, and clearance of, foreign substances (chemical and cellular antigens) that either penetrate the protective body barriers of skin and mucosal surfaces (transplanted tissue and microorganisms such as bacteria, viruses, parasites) or arise de novo (malignant transformation). The arsenal of the immune response is composed of two major types of lymphocytes that are either B-lymphocytes (B cells, responsible for producing antibodies which attack the invading microorganisms) or the T-lymphocytes (T cells, responsible for eliminating the infected or abnormal target cells) in cooperation with macrophages. The cascade of principal events in the immune system is more fully described by I. Roitt, J. Brostoff and D. Male in "Immunology", 3rd edition, Mosby, 1993 which is herein incorporated by reference, and may be summarized as follows.

The response is initiated by the interaction of an antigen with macrophages and surface antibodies on B cells. The macrophages ingest and process the antigen. The activated macrophages secrete interleukin-1 (IL-1) and tumor necrosis factor (TNF), and display the processed antigen on the cell surface together with a major antihistocompatibility antigen. Both IL-1 and TNF initiate a number of processes involving inflammation. Also, IL-1 induces proliferation of B cells and synthesis of antibodies. But more importantly, IL-1 activates T cells that release a series of lymphokines including interleukin-2 (IL-2) that activate the proliferation of T cells and

cytotoxic lymphocytes. In autoimmune diseases, the system is unable to distinguish between "non-self" antigen and "self" antigen and will start to produce autoantibodies or autoreactive T cells that attack the normal components of the body.

Inflammatory reactions differ not only as to the nature of the triggering event, but also in the types of cells mediating the response and in the biochemical nature of the end effectors. In particular, inflammation mediated by monocyte/macrophage activity can result in severe chronic or fatal conditions, including immune complex-initiated primary inflammatory disorders such as glomerulonephritis, chronic interstitial nephritis, interstitial pneumonitis, Crohn's disease, ulcerative colitis, osteoarthritis, biliary cirrhosis and the like, affecting other organ systems; also including connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus and the like; further including secondary progressive inflammatory diseases in which the central cause of tissue destruction is uncontrolled inflammatory/fibrotic processes regardless of the nature of the initiating insult, for example chronic hepatitis, whether the initial insult be infectious, toxic, alcohol, etc., radiation induced chronic inflammations of lung, kidney, central nervous system, inflammations induced by crystal deposition, such as gout, and various forms of post-traumatic inflammatory injury, such as arthritis. Many prior therapeutic strategies have been directed at alleviating the various symptoms of the diseases, without affecting the process itself.

Leukocyte activation leads to the release of degradative enzymes, the generation of reactive oxygen species and the biosynthesis of locally acting pro-inflammatory antacoids. Among the latter, oxygenated metabolites of arachidonic acid are recognized major products of leukocyte activation and exert potent biological effects on cellular functions. The arachidonate lipoxygenase (LO) family of enzymes catalyze the formation of highly potent biologic mediators in leukocytes and platelets. The predominant LO pathway in polymorphonuclear leukocytes (PMN) and macrophages is 5-LO, leading to the formation of leukotrienes (LTs) and 5-hydroxyeicosatetraenoic acid (5-HETE) (Samuelson, B. et al. (1987) Science 237:1171-1176). The sulfidopeptide LTs (LTC_4, LTD_4, and LTE_4) and the non-peptidyl LTB_4, elicit potent biological responses: LTC_4 and LTD_4 contract vascular, pulmonary, and gastrointestinal smooth muscle, and increase vascular permeability to macromolecules (Lewis, R. A. et al. (1984) J. Clini. Invest. 73:889-897; Samuelson, B. et al. (1987) supra). LTB_4 has minimal spasmogenic properties. Its primary target appears to be (PMN)s, which express specific high and low affinity receptors for LTB_4. Through

the former, LTB^4 is the most potent chemotactic substance yet described for this cell and also increases PMN aggregation and adhesion to endothelium. Through the latter, it acts as a calcium ionophore, leading to PMN activation, stimulation of phosphoinositide turnover, release of lysosomal enzymes and an increase in oxidative metabolism. In turn, activated PMNs are the best studied source of LTB_4 where its synthesis is coupled to activation of protein kinase C.

Direct effects of LTC_4, LTD_4 and LTB_4 on normal and inflamed glomerulus have been measured. LTA_4 is a product of 5-LO activity and serves as a precursor for both LTC_4 and LTB_4. The former requires the activity of a glutathione-S-transferase while the latter is the product of LTA_4 hydrolase. LTD_4 is the product of a .gamma.-glutamyl transferase removing a glutamyl moiety from LTC_4. LTD_4 has a powerful effect of reducing glomerular capillary ultrafiltration coefficient acting on both normal and inflamed glomeruli. It is believed to be a major mediator of functional deterioration in glomerulonephritis. LTC_4 has been shown to reduce renal blood flow and glomerular filtration rate acting on normal kidney and is considered to act similarly in inflamed glomerulus. By contrast, LTB_4 has little direct effect on normal glomerulus. However it is a powerful chemotactic agent for PMNs. The role of LTB_4 in glomerulonephritis is seen as an indirect amplifier of leukocyte-dependent reductions in glomerular perfusion due to enhancement of PMN recruitment and activation.

An alternative metabolic pathway initiated by 15-lipoxygenase (15-LO) activity leads to compounds having antagonistic effects to the products of 5-LO activity. Hydroperoxidation of arachidonic acid by 15-LO leads to the formation of 15-S-hydroxyeicosatetraenoic acid (15-S-HETE). Dual lipoxygenation at both the 5 and 15 positions in activated neutrophils and macrophages yields a class of "lipoxygenase interaction products" (Samuelson, B. et al. (1987), supra). Like 5-LO, 15-LO gene expression is restricted largely to leukocyte cell lines, but has also been detected in reticulocytes and airway epithelial cells. Using cDNA probes for human 15-LO, gene expression in glomerular cell lines has not been detected by northern analysis. Macrophages are a particularly rich source of 15-LO and hence of 15-S-HETE and LXs. Three biologically active lipoxins have been identified. LXA_4, (55,6R,155)-5,6,15-trihydroxy-7,9,13-trans-11-cis-eicosatetraenoic acid, LXB_4 (55,14R,155)-5,14,15-trihydroxy-6,10,12-trans-8-cis-eicosatetraenoic acid, and 7-cis-11-trans-LXA_4 (Samuelson, B. et al. (1987), supra; Nicolau, K. C. et al. (1989) Biochem. Biophys. Acta 1003:44-53;

the pharmacological profile of their renal actions has been characterized recently (Katoh, T. et al. (1992) Am. J. Physiol. 263:F436-442). Lipoxin synthesis, like that of leukotrienes, can also occur via transformation of leukocyte-generated LTA_4 by either 15-LO or 12-LO in adjoining cells, such as mesangial cells or platelets.

Evidence for a generalized anti-inflammatory role for 15-LO products has been derived from clinical observations and experimental studies in vivo and in vitro. Administration of 15-S-HETE causes regression of psoriatic lesions in humans and significantly reduces the clinical severity of a canine arthritis model.

The compound, 15-S-HETE, is a specific antagonist of LTB_4 -induced chemotaxis of PMNs. Other chemotactically-active substances are not inhibited. 15-S-HETE also aborts leukocyte activation, abrogates adhesion of PMNs to endothelium and depresses LTB_4 synthesis by leukocytes. During experimental glomerulonephritis, production of LTB_4 reaches a peak about three hours after injury and declines to baseline levels after about 72 hours. In contrast, 15-S-HETE levels increase gradually over time up to two weeks, reaching levels consistent with the amounts required to achieve the antagonistic effects just described. The kinetics are consistent with the view that a slower-acting 15-LO pathway functions to inhibit and limit the intensity and scope of an inflammatory process, once the process has been initiated. The lipoxins, especially LXA_4, also have significant anti-inflammatory functions. For example, LXA_4 acts as an antagonist of the leukotrienes, having anti-chemotactic effect, and having direct vasorelaxation activity and augmentation of glomerular filtration rates. LXA_4 acts as a competitive inhibitor of LTD_4 receptor binding. LXA_4 also prevents or inhibits PMN adhesion to mesangial cells.

The manifold response modalities of the immune systems of mammals are regulated by a variety of secreted immunregulatory proteins termed cytokines. These include various colony stimulating factors, chemokines, interleukins and interferon-γ (IFN-γ). The characteristics of a variety of immune-type responses is largely controlled by the cell types involved and the cytokine network associated therewith in each case. For example, the involvement of the Th1 subset of helper T-cells leads to secretion of IFN-gamma and interleukin-2 (IL-2) which appear to promote a delayed-type hypersensitivity response. Another type of response, mediated by Th2 subset of helper T cells, is characterized by secretion of IL-4 and IL-5, which act to promote antibody responses (Mosmann, T. R. et al. (1989) Annu. Rev. Immunol. 7: 145-173). There is a complex

series of positive or negative responses to each set of cytokines by many cell types in the immune system. Much has been learned concerning the function of cytokine networks. However new findings and newly discovered cytokines often require those skilled in the art to revise their theories of cytokine network interactions.

The system of experimentally induced glomerulonephritis in the rat has yielded significant information as to the processes of disease development and the nature of the biochemical mediators of tissue destruction. See Badr, K. (1992) Kidney International 42(Suppl. 38): S-101-S-108, incorporated herein by reference. The presence of immune complexes in the glomerulus, regardless of their sources, routes of formation, or intraglomerular localization, inevitably and necessarily provokes a complement-mediated influx and activation of polymorphonuclear leukocytes (PMN). The very transient nature of the PMN infiltrate (first few hours following immune activation) renders it an infrequent finding in renal biopsies from patients with various forms of glomerulonephritis, leading to under-appreciation of the potential role of this early inflammatory event in the eventual outcome of disease. PMNs are, however, detected frequently when biopsies are performed during ongoing acute injury such as in patients with post-infectious glomerulonephritides. Characteristically, this initial wave of neutrophil infiltration/activation is replaced by monocyte infiltration and macrophage proliferation and activation. During this secondary ("autologous") phase, it is postulated that injury might be perpetuated not only by the consequences of activation/proliferation of macrophages and indigenous glomerular cells (particularly mesangial and epithelial cells), but also by fresh immune reactions to neo-antigens from host tissue exposed as a result of proteolytic and lipid peroxidative consequences of initial leukocyte activation and degranulation. The number of participating cells in the more chronic phase of immune injury, the interactions among these "stimulated" cell populations, and, consequently, the myriad of peptide and lipid-derived mediators which underlie cellular injury and the eventual replacement of normal glomerular architecture by extracellular matrix (fibrosis), is staggering. While strategies aimed at arresting glomerular injury by targeting the mediators of matrix expansion and scar formation show promise, the complexity of the "mediator soup" during this phase of injury and the various cell populations involved (including tubulointerstitial elements) present serious theoretical and practical obstacles to the development of effective therapeutic interventions.

Targeting the mechanisms which govern the severity of early immune-mediated injury rests on the premise that those diseases which most commonly lead to renal failure due to immune deposition are, for the most part, progressive over months to years, suggesting incremental phases of nephron loss. Evidence from pathologic examinations in several forms of glomerulonephritis indicates that injury is heterogeneous: the number of affected versus healthy glomeruli varies among patients, as well as over time in individual patients. Moreover, within individual glomeruli, lesions are often segmental with inflammatory reactions present in certain lobules, while others are totally normal. These data, as well as a clinical course characterized by steadily diminishing renal reserve over highly varying periods of time, suggest strongly that, in an individual patient, "early" injury is occurring continuously in some fixed proportion of nephrons. It is therefore reasonable to predict that institution of therapy which specifically targets those early events will arrest initial injury in those nephrons, albeit small in number, in which it is underway and, more importantly, prevent or abort its development in intact nephrons, despite the potential continued deposition or formation of immune complexes in these normal glomeruli. This latter assumption is based on the dramatic evidence from experimental studies indicating that mere deposition of antigen-antibody complexes in the glomerular capillary wall or mesangium, in the absence of cellular infiltration (as in leukocyte- or complement-depleted animals) or the capacity to generate arachidonate metabolites (as in fatty acid deficient animals), is without any detrimental acute or chronic consequences to glomerular structure and functions.

Each element in the cascade of the immune response may be considered as a potential site for pharmacological intervention. For example, adrenocorticosteroids act in the first stages of the immune response, interact with the macrophages and, inhibit the synthesis and release of IL-1. Other immunosuppressive agents used in the treatment of autoimmune diseases have been identified, such as azathioprine and methotrexate for rheumatoid arthritis, cyclophosphamide for nephritic conditions of immune origin, and cyclosporin for rheumatoid arthritis, uveitis, early onset insulin dependent diabetes mellitus, psoriasis, nephritic syndrome and aplastic anemia.

In addition, immunosuppressive agents have proved to be useful in preventing and treating organ transplantation rejection that may occur in allograft transplantation. In allograft transplantation one person donates an organ to a genetically disparate individual while in xenograft transplantation an organ of one species is transplanted into a member of

another species. In those cases, the use of cyclosporin has shown a real improvement in the condition of the person receiving the organ. However, the therapeutic index of the available immunosuppressive drugs is narrow, none of the drugs are completely effective and their use has been limited by severe toxicity.

Autoimmune disease results from the immune system attacking the body's own organs or tissues, producing a clinical condition associated with the destruction of that tissue. An autoimmune attack directed against the joint lining tissue results in rheumatoid arthritis; an attack against the conducting fibers of the nervous system results in multiple sclerosis. The autoimmune diseases most likely share a common pathogenesis and the need for safe and effective therapy.

Rheumatoid arthritis is one of the most common of the autoimmune diseases. Current treatments utilize three general classes of drugs (Schumacher, H. R. ed., Primer on the Rheumatic Diseases, Ninth edition, Arthritis Foundation, Atlanta, Ga. (1988): anti-inflammatory agents (aspirin, non-steroidal anti-inflammatory drugs and low dose corticosteriods); disease-modifying antirheumatic drugs, known as "DMARDs" (anti-malarials, gold salts, penicillamine, and sulfasalazine) and immunosuppressive agents (azathioprine, chlorambucil, high dose corticosteroids, cyclophosphamide, methotrexate, nitrogen mustard, 6-mercaptopurine, vincristine, hydroxyurea, and cyclosporin A). None of the available drugs are completely effective, and most are limited by severe toxicity.

In addition to their use in treating autoimmune conditions, immunosuppressive agents have also been used in treating or preventing transplantation rejection. Organ transplantation involving human organ donors and human recipients (allografts), and non-human primate donors and human recipients (xenografts), has received considerable medical and scientific attention (Roberts, J. P., et al., Ann. Rev. Med., 40:287 (1989);

as cyclosporin A, which specifically inhibits T cell activation, and specific antibodies directed against T lymphocytes or surface receptors that mediate their activation (Briggs J. D., Immunology Letters Jul, 29(1-2):89-94 (1991). All of these drug therapies are limited in effectiveness, in part because the doses needed for effective treatment of transplant rejection may increase the patient's susceptibility to infection by a variety of opportunistic invaders, and in part because of direct toxicity and other side effects. For example, cyclosporin A, currently the most commonly used agent, is significantly toxic to the kidney. This nephrotoxicity limits the quantity of drug that can be safely given.

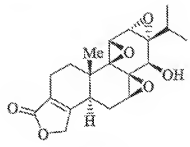
Many useful pharmaceutical agents are derived from plants. In some cases, the plant-derived compound provides a drug lead that is then chemically modified to improve its pharmacological activity and/or simplify its structure for chemical synthesis. In many cases, e.g., where the plant-derived compound is a complex structure, chemical synthesis is impractical, and the compound must be obtained by direct extraction from plants. If the plant is in short supply, or a complex purification scheme is required, or the yield is low, direct extraction from plants may not be practical.

Production of pharmaceutical agents using plant cell cultures has been reported for only a few cases. In general, obtaining what are usually complex compounds by this approach has not been feasible to date.

One plant that illustrates the potential for plant secondary metabolites as useful pharmaceutical agents, and also the difficulty of producing the plant products in practical yields, is Tripterygium wilfordii (TW). A number of compounds having immunosuppressive or other activities have been isolated from extracts of root tissues from TW, including tripterinin (PCT Application PCT/US94/02540), 16-hydroxytriptolide (Ma, 1991a; 1992a), triptriolide (Ma, 1991b), celastrol (Zhang, 1986a,b), triptchlorolide (Zhang, 1992), triptophenolide (Deng, 1992), triptonide (Wu, 1992), tripterine (Zhang, 1990a), tripterygic acid (Zhang, 1990b), sesquiterpene alkaloids (Ya, 1990), isowilfordine (Ya, 1991), sesquiterpene esters (Takaishi, 1990; 1991a; 1992a), sesquiterpene polyol esters (Takaishi, 1991b,c), phenanthrene derivatives (Takaishi, 1991d) tripterygone (Zhang, 1991), salasperinic acid (Chen, 1992), other diterpene lactone epoxide compounds (Zheng, 1991; Ma, 1992b), and diterpene quinones (Shen, 1992; Takaishi, 1992b; Shishido, 1993).

It has now been discovered that various extracts from the poisonous plant Tripterygium wilfordii play an important part in autoimmune and inflammatory

suppression, in particular, triptolide. Triptolide contains and unusual triepoxide moiety and an α,β unsaturated γ-lactone in the diterpene skeleton, and it has potent antileukemic and immunosuppressive activities.



Triptolide

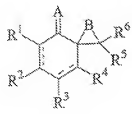
However, in most cases, these compounds are structurally complex molecules which are difficult to purify in useful quantities from plants, and difficult or impossible to synthesize in practical yields. The activity from the crude compounds found in T. wilfordii shows activity, however after purification the activity decreases. The isolated compounds have also been shown to decompose over time and the process is quite slow. At present, it is not known whether cultured cells from T. wilfordii could be induced to produce any of these compounds in commercially useful amounts.

It would therefore be desirable to provide immunosuppressive compounds by methods that overcome the limitations noted above. Additionally, it is further desired to provide immunosuppressive compounds having improved water solubility and low toxicity. At the same time it would be advantageous to discover additional plant-derived compounds, or mimics thereof, with therapeutically useful properties. In addition, it would be desirable for such compounds to exhibit immunosuppressive activity in their water soluble form, or to be convertible to an immunosuppressive form by metabolic processes in vivo or in vitro.

SUMMARY OF THE INVENTION

The present invention provides novel compounds, pharmaceutical compositions and methods for the treatment or prophylaxis of autoimmune or inflammatory disorders. These compounds may act by inducing 15-lipoxygenase (15-LO) in the treatment of such disorders.

In particular, compounds are provided of the formula (I)-(XX):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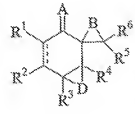
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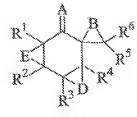
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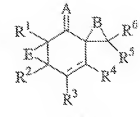
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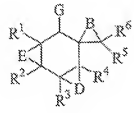
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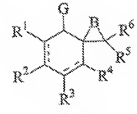
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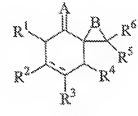
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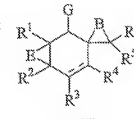
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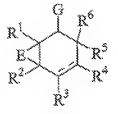
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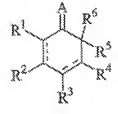
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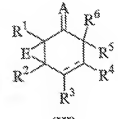
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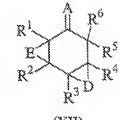
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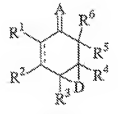
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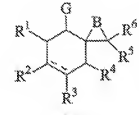
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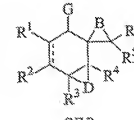
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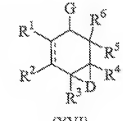
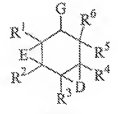
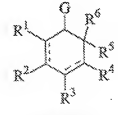

(XVI)


(XVII)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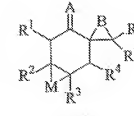
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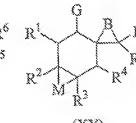

(XX)

and their pharmaceutically acceptable salts and/or prodrugs, thereof, wherein:

each dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

each A, B, D, E and M is independently O, S, NR^7 or CR^7R^8;

each G is independently OR^{11}, $NR^{11}R^{12}$ or SR^{11};

each R^1, R^2, R^3, R^4, R^5 and R^6 is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In a preferred embodiment, the compound exhibits an EC_{50} of less than 25, 15, 10, 5 or 1 micromolar.

In another further embodiment of the present invention is to provide a novel and efficient method for the synthesis of the compounds.

In yet another embodiment of the invention, the compounds of the present invention are administered optionally in a pharmaceutically acceptable carrier or diluent.

In yet another embodiment, the active compound can be administered in combination or alternation with another immunosuppressant or anti-inflammatory agent. In combination therapy, effective dosages of two or more agents are administered together, whereas during alternation therapy an effective dosage of each agent is administered serially. The dosages will depend on absorption, inactivation and excretion

rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

In yet another embodiment of the invention, compositions comprising the compounds of the present invention, optionally in a pharmaceutically acceptable carrier or diluent, in combination with another immunosuppressant or anti-inflammatory agent are provided.

In yet another embodiment, a method for the treatment or prophylaxis of autoimmune or inflammatory disease in a host is provided, comprising administering an effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, optionally in combination or alternation with one or more other immunosuppressant or anti-inflammatory agent.

In yet another embodiment, a method for the treatment or prophylaxis of autoimmune or inflammatory disease in a host is provided, comprising administering a pharmaceutical composition comprising an effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, in combination with one or more other immunosuppressant or anti-inflammatory agent.

In yet another embodiment, a use of an effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, optionally in combination or alternation with one or more other immunosuppressant or anti-inflammatory agent for the simultaneous, separate or sequential treatment or prophylaxis of autoimmune or inflammatory disease in a host is provided.

In yet another embodiment, a use of an effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, optionally in combination or alternation with one or more other immunosuppressant or anti-inflammatory agent in the manufacture of a medicament for the simultaneous, separate or sequential treatment or prophylaxis of autoimmune or inflammatory disease in a host is provided.

Brief Description of the Figures

Figure 1 is a nonlimiting example of the general synthesis for the intermediates of triptolide derivatives.

Figure 2 is a nonlimiting example of the general stereospecific synthesis for triptolide derivatives from intermediates.

Figure 3 illustrates one embodiment of the synthesis of triptolide derivatives according to the present invention.

Figure 4 is a nonlimiting example of general methodologies that can be used to obtain different epoxides of the present invention.

Detailed Description of the Invention

The present invention provides novel compounds, pharmaceutical compositions and methods for the treatment autoimmune and inflammatory disorders. In particular, the present invention relates to novel triptolide derivatives and compositions for the inducement of 15-lipoxygenase (15-LO) in the treatment of autoimmune and anti-inflammatory disorders.

In a preferred embodiment, the compound exhibits an EC_{50} of less than 25, 15, 10, 5 or 1 micromolar.

In another further embodiment of the present invention is to provide a novel and efficient method for the synthesis to the compounds previously mentioned.

In yet another embodiment of the invention, the compounds of the present invention are administered optionally in a pharmaceutically acceptable carrier or diluent.

In yet another embodiment, the active compound can be administered in combination or alternation with another immunosuppressant or anti-inflammatory agent. In combination therapy, effective dosages of two or more agents are administered together, whereas during alternation therapy an effective dosage of each agent is administered serially. The dosages will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to

be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

In yet another embodiment of the invention, compositions comprising the compounds of the present invention, optionally in a pharmaceutically acceptable carrier or diluent, in combination with another immunosuppressant or anti-inflammatory agent are provided.

In yet another embodiment, a method for the treatment or prophylaxis of autoimmune or inflammatory disease in a host is provided, comprising administering an effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, optionally in combination or alternation with one or more other immunosuppressant or anti-inflammatory agent.

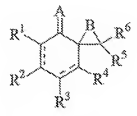
In yet another embodiment, a method for the treatment or prophylaxis of autoimmune or inflammatory disease in a host is provided, comprising administering a pharmaceutical composition comprising an effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, in combination with one or more other immunosuppressant or anti-inflammatory agent.

In yet another embodiment, a use of an effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, optionally in combination or alternation with one or more other immunosuppressant or anti-inflammatory agent for the simultaneous, separate or sequential treatment or prophylaxis of autoimmune or inflammatory disease in a host is provided.

In yet another embodiment, a use of an effective amount of an active compound of the present invention, optionally in a pharmaceutically acceptable carrier, optionally in combination or alternation with one or more other immunosuppressant or anti-inflammatory agent in the manufacture of a medicament for the simultaneous, separate or sequential treatment or prophylaxis of autoimmune or inflammatory disease in a host is provided.

I. Compounds of the Present Invention

In one embodiment of the present invention, a structure of the formula (I) is provided:



(I)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

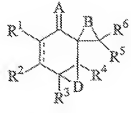
A and B are independently O, S, NR^7 or CR^7R^8;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9 and R^{10} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (II) is provided:



(II)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

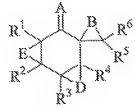
A, B and D are independently O, S, NR^7 or CR^7R^8;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9 and R^{10} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (III) is provided:



(III)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

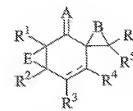
A, B, D and E are independently O, S, NR^7 or CR^7R^8;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9 and R^{10} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (IV) is provided:



(IV)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

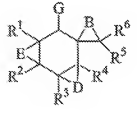
A, B and E are independently O, S, NR^7 or CR^7R^8;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9 and R^{10} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (V) is provided:



(V)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

B, D and E are independently O, S, NR^7 or CR^7R^8;

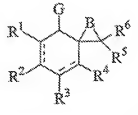
G is OR^{11}, $NR^{11}R^{12}$ or SR^{11};

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (VI) is provided:



(VI)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

B is O, S, NR^7 or CR^7R^8;

G is OR^{11}, $NR^{11}R^{12}$ or SR^{11};

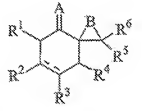
R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine,

hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (VII) is provided:



(VII)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

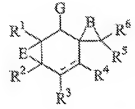
A and B are independently O, S, NR^7 or CR^7R^8;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9 and R^{10} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (VIII) is provided:



(VIII)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

B and E are independently O, S, NR^7 or CR^7R^8;

G is OR^{11}, $NR^{11}R^{12}$ or SR^{11};

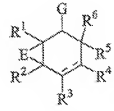
R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered

ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (IX) is provided:



(IX)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

E is O, S, NR^7 or CR^7R^8;

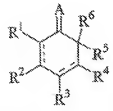
G is OR^{11}, $NR^{11}R^{12}$ or SR^{11};

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (X) is provided:



(X)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

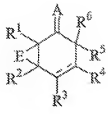
A is O, S, NR^7 or CR^7R^8;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9 and R^{10} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (XI) is provided:



(XI)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

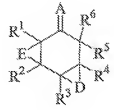
A and E are independently O, S, NR^7 or CR^7R^8;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9 and R^{10} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (XII) is provided:



(XII)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

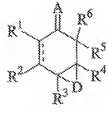
A, D and E are independently O, S, NR^7 or CR^7R^8;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9 and R^{10} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (XIII) is provided:



(XIII)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

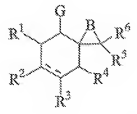
A and D are independently O, S, NR^7 or CR^7R^8;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9 and R^{10} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residne of a natural or syntbetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (XIV) is provided:



(XIV)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

B is O, S, NR^7 or CR^7R^8;

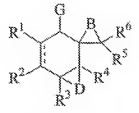
G is OR^{11}, $NR^{11}R^{12}$ or SR^{11};

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (XV) is provided:



(XV)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

B and D are independently O, S, NR^7 or CR^7R^8;

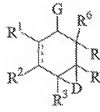
G is OR^{11}, $NR^{11}R^{12}$ or SR^{11};

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (XVI) is provided:



(XVI)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

D is O, S, NR^7 or CR^7R^8;

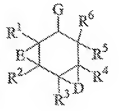
G is OR^{11}, $NR^{11}R^{12}$ or SR^{11};

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (XVII) is provided:



(XVII)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

D and E are independently O, S, NR^7 or CR^7R^8;

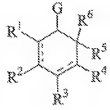
G is OR^{11}, $NR^{11}R^{12}$ or SR^{11};

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (XVIII) is provided:



(XVIII)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

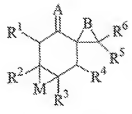
G is OR^{11}, $NR^{11}R^{12}$ or SR^{11};

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (XIX) is provided:



(XIX)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

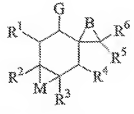
A, B and M are independently O, S, NR^7 or CR^7R^8;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9 and R^{10} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In another embodiment of the present invention a structure of the formula (XX) is provided:



(XX)

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

The dotted line indicates the presence of either a single or double bond, wherein the valences of a single bond are completed by hydrogens;

B and M are independently O, S, NR^7 or CR^7R^8;

G is OR^{11}, $NR^{11}R^{12}$ or SR^{11};

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, carbonyl, carboxylic acid, ester, carbamate, amide, amine, hydroxyl, alkoxide, nitro, cyano, azide, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, phosphonyl, phosphinyl, phosphoryl, phosphine, a residue of a natural or synthetic amino acid, a residue of a natural or synthetic carbohydrate or XR^9 (wherein X = O, S or NR^{10});

alternatively, one or more of R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5, or R^5 and R^6, come together to form a bridged compound, preferably as a 3, 5, 6 or 7 membered ring, to form a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heterocyclic, heteroaryl or heteroaromatic; and

each R^7, R^8, R^9, R^{10}, R^{11} and R^{12} is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaryl, heteroaromatic, alkcarbonyl, a residue of a natural or synthetic amino acid or a residue of a natural or synthetic carbohydrate.

In a sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A and B are independently O, S, NR^7 or CR^7R^8;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{15}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = O;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = NR^{19}.

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = CR^8R^9.

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide,

a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, CR^{15}=CR^{16}, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = S.

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{15}R^{16}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = S, B = O.

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{15}R^{16}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = S, B = NR^8.

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide,

a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = S, B = CR^8R^9.

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = S, B = S.

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = CR^8R^9; B = O.

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide,

a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = CR^8R^9, B = NR^{10};

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

$A = CR^8R^9$, $B = CR^{21}R^{22}$.

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{12}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In another sub-embodiment, a structure of the formula (I) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

$A = CR^8R^9$, B = S.

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide,

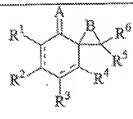
a residue of a natural or synthetic amino acid, or carbohydrate or XR^{13} (X = O, NR^{14} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{22} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$;

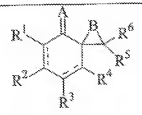
the dotted line indicates the presence of either a single or double bond, wherein in the presence of a single bond, the valences are completed with hydrogens.

In a particular embodiment of the present invention, the compounds of the formula (I) are the following species:



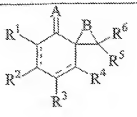
(I)

A	B	R^1	R^2	R^3	R^4	R^5	R^6
O	O	Me	H	H	H	Me	Me
O	O	*i*-Pr	H	H	H	Me	Me
O	O	Ph	H	H	H	Me	Me
O	O	Me	Me	H	H	Me	Me
O	O	*i*-Pr	Me	H	H	Me	Me



(I)

A	B	R^1	R^2	R^3	R^4	R^5	R^6
O	O	Ph	Me	H	H	Me	Me
O	O	Me	H	Me	H	Me	Me
O	O	*i*-Pr	H	Me	H	Me	Me
O	O	Ph	H	Me	H	Me	Me
O	O	Me	H	H	Me	Me	Me
O	O	*i*-Pr	H	H	Me	Me	Me
O	O	Ph	H	H	Me	Me	Me
O	O	Me	H	CH_2Ph	H	Me	Me
O	O	*i*-Pr	H	CH_2Ph	H	Me	Me
O	O	Ph	H	CH_2Ph	H	Me	Me
O	CH_2	Me	H	H	H	Me	Me
O	CH_2	*i*-Pr	H	H	H	Me	Me
O	CH_2	Ph	H	H	H	Me	Me
O	CH_2	Me	Me	H	H	Me	Me
O	CH_2	*i*-Pr	Me	H	H	Me	Me
O	CH_2	Ph	Me	H	H	Me	Me
O	CH_2	Me	H	Me	H	Me	Me
O	CH_2	*i*-Pr	H	Me	H	Me	Me
O	CH_2	Ph	H	Me	H	Me	Me



(I)

A	B	R^1	R^2	R^3	R^4	R^5	R^6
O	CH_2	Me	H	H	Me	Me	Me
O	CH_2	*i*-Pr	H	H	Me	Me	Me
O	CH_2	Ph	H	H	Me	Me	Me
O	CH_2	Me	H	CH_2Ph	H	Me	Me
O	CH_2	*i*-Pr	H	CH_2Ph	H	Me	Me
O	CH_2	Ph	H	CH_2Ph	H	Me	Me

In a sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = O, D = O;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S).

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = NR^{10}, D = O;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S).

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = CR^8R^9, D = O;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S).

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = S, D = O;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S).

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl,

carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = CR^5R^9, B = O, D = O;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S).

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = CR^8R^9, B = $CR^{18}R^{19}$, and D = O;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S).

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = CR^8R^9, B = $CR^{18}R^{19}$, and D = O;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S).

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl,

carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}=CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = CR^8R^9, B = S, and D = O;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S).

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}=CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = O, D = CR^8R^9;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S).

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = NR^{10}, D = CR^8R^9;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl,

sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{15} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = CR^8R^9, D = $CR^{18}R^{19}$;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = O, B = S, D = CR^8R^9;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{15}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

A = CR^8R^9; B = O, D = $CR^{18}R^{19}$;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl,

sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

$A = CR^8R^9$, $B = NR^{10}$, $D = CR^{18}R^{19}$;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

$A = CR^9R^9$, $B = CR^{18}R^{19}$, $D = CR^{20}R^{21}$;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, carboxylic acid, amide, nitro, cyano, azide, phosphonyl, phosphinyl, phosphoryl, phosphine, carbamate, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{18} (X = O, NR^{19} or S);

R^1 and R^2, R^2 and R^3, R^3 and R^4, R^4 and R^5 and R^5 and R^6 can also each be comprised of one or two $CR^{13}R^{14}$ groups, connected by a tether, independently selected from $CR^{15}R^{16}$, $CR^{15}R^{16}CR^{17}R^{18}$, $CR^{15}{=}CR^{16}$, $CR^{15}R^{16}O$ or $CR^{15}R^{16}NR^{17}$; and

the dotted line indicates the presence of either a single or double bond, wherein the presence of a single bond, the valences are completed by hydrogens.

In another sub-embodiment, a structure of the formula (II) is given wherein the compound or its pharmaceutically acceptable salts or prodrug is defined as follows:

$A = CR^8R^9$, $B = S$, $D = CR^{18}R^{19}$;

R^1 is selected independently from the groups that include hydrogen, alkyl, cycloalkyl, aryl, alkaryl, arylalkyl, heterocyclic, ester, alkcarbonyl, carbonyl, halide, a residue of a natural or synthetic amino acid, or carbohydrate or XR^{11} (X = O, NR^{12} or S);

R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently are selected from the groups that include hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl, arylalkyl, heterocyclic, sulfonyl,